REMARKS

I. Claim Status

Claims 26-27 and 29-32 are pending and under examination. Reconsideration of the pending claims in view of the following arguments and remarks is respectfully requested.

Claim 29 has been amended to recite a reference sequence for Dau c 1.

Claims 30-32 have been amended for correct form and grammar to recite "and" before the last secondary mutation listed in each claim.

No new matter is added by way of the present amendments.

The Examiner has stated that claims 30-32 are objected to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

II. Rejections Under 35 U.S.C. 112§, First paragraph (Enablement)

Claims 26-27 and 29 have been rejected under 35 U.S.C. §112, first paragraph because the Examiner states that the specification, while being enabling for a modified Dau c 1 scaffold protein depicted as SEQ ID NO:4 and comprising at least two primary mutations selected from the group recited in claims 30-32, allegedly does not reasonably provide enablement for variants of a scaffold protein Dau c 1 having a three-dimensional folding pattern that is structurally similar to that of the naturally occurring allergen, the protein variant comprises two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to the amino acid residue or residues in the corresponding position in the naturally occurring allergen.

According to the Examiner, one skilled in the art would be unable to use the full breadth of the claimed invention without conducting an undue amount of research. The Examiner bases her argument on the following points:

1. the difficulty in ascertaining the precise location to make the substitution mutations;

2. the art recognized problem concerning the unpredictability of which amino acid substitution mutations result in the desired altered Ig E binding;

3. data from the art and applicant's specification, indicating that a skilled artisan would be unable to make and use the full breadth of the claimed invention without conducting an undue amount of research.

As an initial matter, claims 26-27 recite recombinant protein variants comprising SEQ ID NO:2 or SEQ ID NO:3. A detailed description is provided in the specification at paragraphs 119-120 of the Mal d 1 protein variant (rMal d 1 (2781) comprising SEQ ID NO:2:

> In another specific embodiment, a protein variant of a Mal d 1 protein variant (rMal d 1 (2781) comprises the sequence defined in SEQ ID NO 2:
>
> GVYTYENEYTSEIPPPRLFKAFVLDADNLIPKIAPQAIKHAENIEGN
> GGPGTIKKITFGEGSQYKYVKHRIDSVDHANYSYAYTLIEGDALT
> DTIEKVSYETKLVASGSGSIIKSISHYHTKGDVEIMEEHVKAGKEK
> AHGLFKLIESYLKDHPDAYN,
>
> said variant comprising the following primary mutations: I43N, L44I, D47N, G65K, K70R, Q76H. The rMal d 1 (2781) variant is an example of a protein variant according to the present invention that has increased Bet v 1 specific IgE reactivity in comparison with the "native" Mal d 1 2620. This is illustrated in detail in the Examples.

A description of Mal d 1 protein variant (rMal d 1 (2762)) comprising SEQ ID NO 3 is provided in the specification at paragraphs 121-122:

In yet another specific embodiment, a protein variant of a Mal d 1 protein variant (rMal d 1 (2762)) comprises the sequence as defined in SEQ ID NO 3:

GVYTYENEYTSVIPPARLFKAFVLDADNLIPKIAPQAIKHAEILEG
DGGPGTIKKITFGEGSQYGYVKHKIDSVDEANYSYAYTLIEGDAL
TDTIEKVSYETKLVATPDGGSIIKSISHYHTKGDVEIMEEHVKAGK
EKAHGLFKLIESYLLDHSDAYN,

said variant comprising the following mutations: E12V, P16A, K152L, P155S, S107T, G108P, +109D, S110G. "+" means in this connection insertion of an amino acid at the indicated position. The rMal d 1 (2762) variant is an example of a protein variant according to the present invention that has increased Bet v 1 specific IgE reactivity in comparison with the "native" Mal d 1 2620. This is illustrated in detail in the Examples.

Additionally, these protein variants exhibit the ability to induce a protective immune response to a naturally occurring allergen-- since they were tested and shown in the Examples to exhibit increased Bet v 1 specific IgE reactivity in comparison with that of the "native" Mal d 1 2620 (See Example 5). This binding ability provides a protective immune response since the variants can compete with IgE binding upon allergen exposure leading to a reduced risk of inducing IgE-mediated allergic responses.

Thus, in view of the extensive guidance provided in the specification, claims 26-27 are fully enabled and their rejection under 35 U.S.C. §112 should be withdrawn.

With regard to claim 29, Applicants point to the teachings in the specification relating to determining suitable positions for amino acid substitutions and for determining and testing increased binding affinity for IgE:

- suitable mutations (**page 40 lines 16-26, page 42 lines 12-28, page 41 lines 4-7**);
- suitable homologous or identical amino acids for substitution is (**page 15-23, page 59 lines 5-7**) and
- exemplary increased IgE affinity and/or binding capacity (**page 28 lines 10-21, example 5**).

Additionally, in order to expedite prosecution and without conceding the validity of the rejection, claim 29 has been amended to recite a reference sequence for Dau c 1 (SEQ ID NO:4). Support for this amendment may be found in the Sequence Listing and in the sequence corresponding to Accession No. T14325.

Furthermore, the present invention involves protein structure/function and design, a mature field of technology that has benefited in the last 20 years by the use of computer programs for predicting 3-D protein structure. The specification provides description for the features of the genus characterizing the protein variants encompassed by the present invention. Numerous species that meet the claimed features are described throughout the specification (see page 29-36) including, *e.g.*, Mal d 1 variant 2760 (modifying an allergen-like epitope to reduce cross-reactivity of the scaffold i.e., secondary substitutions); Mal d 1 variants 2781 and 2762 (modifying an non-allergen like surface on the scaffold to introduce an allergen-like epitope i.e., primary substitution). One skilled in the art can readily follow the extensive guidance in the specification describing suitable locations, suitable substitutions, and exemplary species to arrive at the claimed protein variants of a scaffold protein Dau c 1.

The Examiner cites Reese et al., *J. Immunol.* 2005, 175:8354-8364 (in particular at Table I and Fig. 2) as supportive of the assertion that even when a precise amino acid within the epitope to be altered is identified, the choice of what the amino acid should be mutated to is not predictable since some substituted amino acids reduce IgE binding while others have no effect or unexpectedly increase IgE binding. In response, Applicants point out that it is well within the ability of one ordinarily skilled in the protein structure/function and molecular biology art to make a substitution according to the extensive guidance provided in the specification, and in particular on the pages noted above, and then to determine whether the resulting variant has the desired binding affinity to

IgE according to standard methods, including ones described in the specification at least on page 28 lines 10-21, and in Example 5, as described above.

The extensive teachings of the specification and examples reduced to practice provide more than adequate enablement and written description for the full scope of what is claimed.

The Examiner cites Niu et al., *Resp. Med.* E.pub. Jan. 3, 2006; for supporting the proposition that immunotherapy is not an effective treatment for all individuals, and that even for those for whom treatment is effective, that allergic symptoms persist at a diminished level.

Applicants point out that Niu describes results of studies using a particular type of immunotherapy-- sublingual immunotherapy. The results in Niu indicate that a 24-week course of sublingual immunotherapy is of clinical benefit to the asthmatic children tested in Taiwan. Importantly, the pending claims do not require complete protection or elimination of all allergy symptoms. Instead, the claims call only that for the recombinant protein variant to have "the ability to induce a protective immune response to a naturally occurring allergen." Niu is supportive of the general applicability of immunotherapy for treating various allergic conditions. However, as a description of a clinical study using sublingual immunotherapy, Niu is not probative of enablement of the pending claims.

Regarding the term "protective immune response," the Examiner previously raised this issue in an office action from May 19, 2005. This rejection was overcome in Applicants' response filed Oct. 17, 2005. A copy of the Oct. 17, 2005 response is attached. The relevant portion of the response is repeated hereinbelow:

> Applicants respectfully point out that the term "protective immune response" (the complete term recited in pending claim 1) is particularly defined in this application, as it is used in the vaccine art. *See*, in particular, in the application as originally filed at page 43, lines 1-7. This definition makes it clear that the term, as used in this application, specifically refers to responses resulting in the production of mediator substances, such as cytokines and antibodies, that is well known to occur upon the

stimulation of leukocytes (including T and B lymphocytes) and whose production neutralizes a particular antigen. Applicants therefore submit that the term is fully definite within the context of the application.

With regard to IgE antibodies mentioned by the Examiner, Applicants point out that IgG antibodies (and not IgE antibodies) are the ones that are generated in response to the inventive recombinant proteins and the IgG antibodies play a role in providing the desired protective immune response of the present invention. Additionally, the Examiner states that Applicants' definition also involves the activation of T cells, and that the number of stimulated T-cells necessary to raise a "protective" immune response is not discussed. Applicants note that there is no need to describe any particular number of T-cells or B cells that are stimulated using the inventive recombinant proteins. Applicants note that there are many examples throughout the specification of the use of "protective" consistent with its definition and as it is used in the vaccine art, for example with reference to the published application:

para 37: Introduction of mutations in the scaffold protein, introducing or modulating or eliminating existing antibody binding surface contours or epitopes homologous to structures of the allergen, results in creation of stable protein variants, ***capable of raising a protective immune response*** and with a lowered risk of inducing side-effects, since the mutated scaffold protein variant exhibits a lower antibody reactivity compared to the natural allergen.

"The purpose is to generate surface contours of the scaffold protein having similarity to the naturally occurring allergen in question, in order to enable stimulation of immune responses that will generate ***protective IgG antibodies*** with the ability to block IgE binding to the natural allergen and thereby alleviate or cure allergy symptoms."

para 42: The affinities of the IgE interactions should be reduced to a level limiting or abolishing the risk of triggering effector cell degranulation, while at the same time retaining the capacity to induce formation of ***protective antibodies reactive with the allergen*** in question.

para 79: The idea behind the invention is thus that a relatively small number of mutations are generally required in order to partly or fully establish allergen specific IgE recognizing contours on the surface of an appropriate scaffold protein. Such molecules have the potential ***of inducing new protective immune***

responses that can compete with IgE binding upon allergen exposure leading to a reduced risk of inducing IgE-mediated allergic responses

para 168: ***Protective immune response***: Raising a protective immune response means to alter the reaction of the immune system towards a naturally occurring allergen in order to avoid the adverse effects associated with allergy. The protective immune response is thought to be mediated largely by generation of a large number of IgG antibodies that presumably block the interaction between allergen and IgE antibodies. A protective immune response most likely also involves stimulation of T-cells.

(*See* Response to Non-Final Office Action of October 17, 2005, copy attached herewith).

****

The Examiner acknowledges on page 5 of the Office Action that "it is clear that one of ordinary skill can ascertain that the instant protein variants are capable of inducing an immune response." In view of the description in the specification as cited above, relating to both the IgG and T cell response, one of ordinary skill can likewise ascertain that the claimed protein variants exhibit "the ability to induce a protective immune response to a naturally occurring allergen." Thus, the term "protective immune response" is clearly defined in the specification. Additionally, it is believed that this issue was previously raised and overcome.

For all the foregoing reasons, Applicants respectfully submit that the rejections under 35 U.S.C. § 112, paragraph 1, have been fully obviated and should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. Applicants reserve the right to pursue the canceled and/or non-elected subject matter in one or more continuation or divisional applications.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: October 29, 2007

Respectfully submitted,

By 

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Application No. (if known): 10/698,855 Attorney Docket No.: 04305/100M237-US1

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MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

on October 17, 2005
Date

Signature

D Beck
Typed or printed name of person signing Certificate

Registration Number, if applicable

Telephone Number

Note: Each paper must have its own certificate of mailing, or this certificate must identify each submitted paper.

Two Month Request for Extension of Time Under 37 CFR 1.136(a) (1 page)
Amendment in Response to Non-Final Office Action (19 pages)
Amendment Transmittal (1 page)
Transmittal (1 page)
Check in the amount of $450.00
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PTO/SB/21 (09-04)
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TRANSMITTAL FORM

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Total Number of Pages in This Submission

Application Number	10/698,855-Conf. #9333
Filing Date	October 31, 2003
First Named Inventor	Jens Holm
Art Unit	1653
Examiner Name	M. M. Tsay
Attorney Docket Number	04305/100M237-US1

ENCLOSURES (*Check all that apply*)

- [ ] Fee Transmittal Form
- [x] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
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- [ ] Terminal Disclaimer
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- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
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- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	DARBY & DARBY P.C.		
Signature			
Printed name	Samuel S. Woodley, Ph.D.		
Date	October 17, 2005	Reg. No.	43,287

PTO/SB/22 (12-04)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2005 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)	Docket Number (Optional) 04305/100M237-US1
Application Number 10/698,855-Conf. #9333	Filed October 31, 2003
For RECOMBINANT PROTEIN VARIANTS	
Art Unit 1653	Examiner M. M. Tsay

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☒	Two months (37 CFR 1.17(a)(2))	$450	$225	$ 450.00
☐	Three months (37 CFR 1.17(a)(3))	$1020	$510	$
☐	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
☐	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 04-0100 . I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 43,287

☐ attorney or agent under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____ .

Signature	October 17, 2005 Date
Samuel S. Woodley, Ph.D.	(212) 527-7610
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of 1 forms are submitted.

AMENDMENT TRANSMITTAL LETTER

Docket No. 04305/100M237-US1

Application No.	Filing Date	Examiner	Art Unit
10/698,855-Conf. #9333	October 31, 2003	M. M. Tsay	1653

Applicant(s): Jens Holm et al.

Invention: RECOMBINANT PROTEIN VARIANTS

TO THE COMMISSIONER FOR PATENTS

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated and is transmitted as shown below.

CLAIMS AS AMENDED

	Claims Remaining After Amendment	Highest Number Previously Paid	Number Extra Claims Present	Rate	
Total Claims	56	- 72 =		x	
Independent Claims	5	- 6 =		x	
Multiple Dependent Claims (check if applicable)		☐			
Other fee (please specify):	Extension for response within second month				450.00
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT:					450.00

[x] Large Entity ☐ Small Entity

☐ No additional fee is required for this amendment.

☐ Please charge Deposit Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

[x] A check in the amount of $ 450.00 to cover the filing fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

[x] The Director is hereby authorized to charge and credit Deposit Account No. 04-0100 as described below. A duplicate copy of this sheet is enclosed.

[x] Credit any overpayment.

[x] Charge any additional filing or application processing fees required under 37 CFR 1.16 and 1.17.

Dated: October 17, 2005

Samuel S. Woodley, Ph.D.
Attorney Reg. No.: 43,287

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DRAFT

Docket No.: 04305/100M237-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jens Holm et al.

Application No.: 10/698,855 Confirmation No.: 9333

Filed: October 31, 2003 Art Unit: 1653

For: RECOMBINANT PROTEIN VARIANTS Examiner: M. M. Tsay

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action mailed by the U.S. Patent and Trademark Office on May 19, 2005, with an extended date for response of Oct. 19, 2005, and in accordance with Rule 116 of the Rules of Practice, please enter the following amendments and consider the accompanying remarks. Included herewith is a separate request for a two-month extension of time. It is believed that no additional fees are due; however, the Commissioner is authorized to charge any deficiencies in the required fees and/or to credit any refund owed to our Deposit Account No. 04-0100.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 11 of this paper.

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph starting at page 30, line 12 with the following paragraph:

--In an embodiment, where rMal d 1 (2620) (database accession number: AJ488060) is the Bet v 1 scaffold protein, a protein variant comprises at least two primary mutations selected from the group consisting of: (E12V, E12I, E12M, E12L), P16A, (H40S, H40T), I43N, L44I, D47N, G65K, K70R, (E76H, E76R, E76K, ~~Q76H~~ E76Q), S107T, G108P, +109D, S110G, E129A, K152L, (P154S, P154T), P155S and optionally one or more secondary mutations are selected from the group consisting of: N28X, preferably N28T, K32X, preferably K32Q, E45S, E96X, +159X. In this context, as well as in the following examples, the first letter and number corresponds to the original amino acid code in a particular amino acid position. The following letter is the amino acid that can be substituted with the original amino acid. Parenthesis means that there are a number of different options when choosing to mutate in a given amino acid position. One of these can be chosen.--

Please replace the paragraph starting at page 31, line 5 with the following paragraph:

--In another specific embodiment, a protein variant of a Mal d 1 protein variant (rMal d 1 (2781)) comprises the sequence defined in SEQ ID NO 2:

GVYTYENEYTSEIPPPRLFKAFVLDADNLIPKIAPQAIKHAENIEGNGGPGTIKKITFGEGSQY
KYVKHRIDSVDHANYSYAYTLIEGDALTDTIEKVSYETKLVASGSGSIIKSISHYHTKGDVEI
MEEHVKAGKEKAHGLFKLIESYLKDHPDAYN,

said variant comprising the following primary mutations: I43N, L44I, D47N, G65K, K70R, ~~Q76H~~ E76Q. The rMal d 1 (2781) variant is an example of a protein variant according to the present invention that has increased Bet v 1 specific IgE reactivity in comparison with the "native" rMal d 1 2620. This is illustrated in detail in the Examples.--

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A recombinant protein variant with the ability to induce a protective immune response to a naturally occurring allergen,

wherein the protein variant is a variant of a scaffold protein, said scaffold protein has a three-dimensional folding pattern that is structurally similar to that of the naturally occurring allergen, compared to the scaffold protein, comprises two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to the amino acid residue or residues in corresponding position in the naturally occurring allergen,

and the recombinant protein variant has, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring allergen.

2. (Original) A protein variant according to claim 1, wherein the protein variant has a reduced ability to induce histamine release compared to the naturally occurring allergen.

3. (Previously presented) A protein variant according to claim 2 wherein the ability to induce histamine release is reduced 2 - 10,000 fold.

4. (Original) A protein variant according to claim 1, which further comprises one or more secondary mutations introducing into the scaffold protein amino acid residues, which are not present in the corresponding position in the naturally occurring allergen.

5. (Previously presented) A protein variant according to claim 1 comprising 2 to 50 primary mutations.

6. (Previously presented) A protein variant according to claim 1, wherein the scaffold protein has a level of amino acid identity with the naturally occurring allergen of between 20 and 60 %.

7. (Original) A protein variant according to claim 1, wherein the protein variant compared to the naturally occurring allergen has a decreased binding capacity with respect to antibodies specific to the naturally occurring allergen.

8. (Previously presented) A protein variant according to claim 1, wherein the said binding capacity is increased to at least 10%, of the antibody binding capacity of the natural allergen.

9. (Original) A protein variant according to claim 1, wherein at least one of the primary mutations is a substitution.

10. (Original) A protein variant according to claim 1, wherein the introduction of at least one of the primary mutations is a deletion and/or an addition.

11. (Previously presented) A protein variant according to claim 1, wherein the deconvoluted CD-spectra of the protein variant deviates less than 30% compared to the deconvoluted CD-spectra of the naturally occurring allergen.

12. (Original) A protein variant according to claim 1, wherein all primary mutations are located within a surface region having an area of about 600-900 $Å^2$.

13. (Original) A protein variant according to claim 1, wherein the primary mutations comprise mutation of surface-exposed amino acids.

14. (Previously presented) A protein variant according to claim 13, wherein the primary amino acid residues to be mutated have a solvent accessibility of above 20 %.

15. (Original) A protein variant according to claim 1, wherein one or more of the mutations are carried out by site-directed mutagenesis.

16. (Original) A protein variant according to claim 1, wherein one or more of the mutations are carried out by DNA shuffling.

17. (Original) A protein variant according to claim 1 obtained by gene library methods.

18. (Canceled)

19. (Previously presented) A protein variant with the ability to induce a protective immune response to a naturally occurring allergen, obtainable by a method comprising the steps of:

- selecting a scaffold protein, said scaffold protein having a three-dimensional folding pattern that is structurally similar to that of the naturally occurring allergen,
- introducing two or more primary mutations, that are spaced by at least one non-mutated amino acid residue, into the scaffold protein, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to the corresponding amino acid residue or residues in the naturally occurring allergen, and
- the protein variant having, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring protein.

20. (Original) A protein variant according to claim 1, wherein the naturally occurring allergen is an inhalation allergen.

21. (Original) A protein variant according to claim 20, wherein the naturally occurring allergen is a pollen allergen.

22. (Original) A protein variant according to claim 21, wherein the naturally occurring allergen is a pollen allergen originating from the taxonomic order of *Fagales*, *Oleales* or *Pinales*.

23. (Original) A protein variant according to claim 22, wherein the naturally occurring allergen is *Bet v* 1.

24. (Original) A protein variant according to claim 23, wherein the scaffold protein is *Mal d* 1.

25. (Currently amended) A protein variant according to claim 24, wherein the *Mal d* 1 scaffold is *Mal d* 1 2620 having Accession No. AJ488060 and wherein at least two primary mutations are selected from the group consisting of: (E12V, E12I, E12M, E12L), P16A, (H40S, H40T), I43N, L44I, D47N, G65K, K70R, (E76H, E76R, E76K, ~~Q76H~~ E76Q), S107T, G108P, +109D, S110G, E129A, K152L, (P154S, P154T), P155S and optionally one or more secondary mutations are selected from the group consisting of: N28X, preferably N28T, K32X, preferably K32Q, E45S, E96X, +159X.

26. (Previously presented) A protein variant (rMal d 1 (2781)) according to claim 24 comprising the sequence defined in SEQ ID NO 2.

27. (Previously presented) A protein variant (rMal d 1 (2762)) according to claim 24 comprising the sequence as defined in SEQ ID NO 3.

28. (Currently amended) A protein variant according to claim 24 wherein the *Mal d* 1 scaffold is *Mal d* 1 2620 having Accession No. AJ488060 and wherein the variant ~~that~~ comprises at least two primary mutations selected from the group consisting of: (E12V, E12I, E12M, E12L), (H40S, H40T), (E76H, E76R, E76K), E129A, (P154S, P154T), and optionally one or more secondary mutations selected from the group consisting of: E8X, N28X, K32X, E96X, +159X.

29. (Original) A protein variant according to claim 23 wherein the scaffold protein of Bet v 1 is Dau c 1.

30. (Currently amended) A protein variant according to claim 29, wherein the Dau c 1 scaffold protein is Accession No. T14325 and wherein at least two primary mutations are selected from the group consisting of: (S12V, S12L, S12I, S12M), S14P, E16A, P105A, A107P, (A148S, A148T), (I151L, I151V, I151M), (N153H, N153K, N153R), (+154S, +154T), (+155D, +155E), +156A, (+157Y, +157F), (+158N, +158Q), (K39S, K39T), (K44E, K44D), (V52I, V52M,

V52L), (I54K, I54R, I54H), (T64K, T64R, T64H), (T65Y, T65F, T65W), (T67K, T67R, T67H), D86E, L91G, (G92D, G92E) and optionally one or more secondary mutations are selected from the group consisting of: K32X, E42X, E59X, R69X, E95X, K122X, E8X, T10X, D25X, D46X, D108X.

31. (Currently amended) A protein variant according to claim 29 wherein the Dau c 1 scaffold protein is Accession No. T14325 and ~~that~~ comprises at least two primary mutations selected from the group consisting of: (S12V, S12L, S12I, S12M), S14P, E16A, P105A, A107P, (A148S, A148T), (I151L, I151V, I151M), (N153H, N153K, N153R), (+154S, +154T), (+155D, +155E), +156A, (+157Y, +157F), (+158N, +158Q) and optionally one or more secondary mutations selected from the groups consisting of: K32X, E42X, E59X, R69X, E95X, K122X.

32. (Currently amended) A protein variant according to claim 29 wherein the Dau c 1 scaffold protein is Accession No. T14325 and ~~that~~ comprises at least two primary mutations selected from the group consisting of: (K39S, K39T), (K44E, K44D), (V52I, V52M, V52L), (I54K, I54R, I54H), (T64K, T64R, T64H), (T65Y, T65F, T65W), (T67K, T67R, T67H), D86E, L91G, (G92D, G92E) and optionally at least one secondary mutation is selected from the group consisting of: E8X, T10X, D25X, K32X, D46X, E59X, E95X, D108X, K122X.

33-51. (Canceled)

52. (Currently amended) A recombinant protein variant with the ability to modulate an immune response to a naturally occurring allergen, wherein

- the naturally occurring allergen is selected from the group consisting of plant, grass, food, and mite allergens,

- the protein variant is a variant of a scaffold protein, said scaffold protein has a three-dimensional folding pattern that is similar to that of a naturally occurring allergen, the protein variant compared to the scaffold protein comprises at least ~~one~~ two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous

to at least one amino acid residue present in the corresponding position in the natural occurring allergen, and

- the protein variant has, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring protein.

53. (Currently amended) A recombinant protein variant with the ability to modulate an immune response to a naturally occurring allergen, wherein

- the protein variant is a variant of a scaffold protein, said scaffold protein has a three-dimensional folding pattern that is similar to that of the naturally occurring allergen,
- the scaffold protein having a level of sequence identity with the naturally occurring allergen of between 30 and 50 %,
- the protein variant compared to the scaffold protein comprises at least ~~one~~ two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to at least one amino acid residue present in the corresponding position in the natural occurring allergen, and
- the protein variant has, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring.

54. (Currently amended) A recombinant protein variant with the ability to modulate an immune response to a naturally occurring allergen, wherein

- the protein variant is a variant of a scaffold protein, said scaffold protein has a three-dimensional folding pattern that is similar to that of a naturally occurring allergen,
- the deconvoluted CD-spectra of the protein variant deviates less than 30%-compared to the deconvoluted CD-spectra of the naturally occurring allergen,

- the protein variant compared to the scaffold protein comprises at least ~~one~~ two or more primary mutations spaced by at least one non-mutated amino acid residue, each primary mutation introducing into the scaffold protein at least one amino acid residue identical or homologous to at least one amino acid residue present in the corresponding position in the natural occurring allergen, and

- the protein variant has, compared to the scaffold protein, an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring protein.

55. (Original) A pharmaceutical composition comprising protein variant according to any one of claims 1, 19 or 52-54 and a pharmaceutically acceptable carrier, excipient, or adjuvant.

56. (Original) A composition according to claim 55 comprising two or more recombinant protein variants, wherein each variant is defined by having at least one primary mutation, which is absent in at least one of the other variants.

57. (Previously presented) A composition according to claim 56 comprising 2 to 12 different protein variants.

58. (Canceled)

59. (Original) The pharmaceutical composition of claim 55 in the form of a vaccine against allergic reactions elicited by a naturally occurring allergen in patients suffering from allergy.

60-72. (Canceled)

73. (Original) A recombinant protein variant according to any one of claims 1, 19 or 52-54 comprising at least one T-cell epitope capable of stimulating a T-cell clone or T-cell line specific for the naturally occurring allergen.

74-75. (Canceled)

76. (Previously presented) A protein variant according to claim 5 comprising 2 to 40 primary mutations.

77. (Previously presented) A protein variant according to claim 5 comprising 3 to 25 primary mutations.

78. (Previously presented) A protein variant according to claim 5 comprising 4 to 15 primary mutations.

79. (Previously presented) A protein variant according to claim 5 comprising 5 to 12 primary mutations.

80. (Previously presented) A protein variant according to claim 6, wherein the scaffold protein has a level of amino acid identity with the naturally occurring allergen of between 30 and 50 %.

81. (Previously presented) A protein variant according to claim 8, wherein the said binding capacity is increased to at least 50% of the antibody binding capacity of the natural allergen.

82. (Previously presented) A protein variant according to claim 8, wherein the said binding capacity is increased to at least 100% of the antibody binding capacity of the natural allergen.

83. (Previously presented) A protein variant according to claim 11, wherein the deconvoluted CD-spectra of the protein variant deviates less than 20% compared to the deconvoluted CD-spectra of the naturally occurring allergen.

84. (Previously presented) A protein variant according to claim 11, wherein the deconvoluted CD-spectra of the protein variant deviates less than 10% compared to the deconvoluted CD-spectra of the naturally occurring allergen.

85. (Previously presented) A protein variant according to claim 14, wherein the primary amino acid residues to be mutated have a solvent accessibility of above 30 %.

86. (Previously presented) A protein variant according to claim 14, wherein the primary amino acid residues to be mutated have a solvent accessibility of above 40 %.

87. (Previously presented) A protein variant according to claim 14, wherein the primary amino acid residues to be mutated have a solvent accessibility of above 50 %.

88. (Previously presented) A recombinant protein variant according to claim 54, wherein the deconvoluted CD-spectra of the protein deviates less than 20% compared to the deconvoluted CD-spectra of the naturally occurring allergen.

89. (Previously presented) A recombinant protein variant according to claim 54, wherein the deconvoluted CD-spectra of the protein deviates less than 10% compared to the deconvoluted CD-spectra of the naturally occurring allergen.

90. (Previously presented) A composition according to claim 57 comprising 3 to 10 different protein variants.

91. (Previously presented) A composition according to claim 57 comprising 4 to 8 different protein variants.

92. (Previously presented) A composition according to claim 57 comprising 5 to 7 different protein variants.

REMARKS

Claims 1-17, 19-32, 52-57, 59, 73, and 76-92 are currently pending in the present application.

Applicants note that the Examiner has withdrawn objections to the drawings and specification and to claims 3 and 30 due to minor informalities or typographical errors. The rejection of claims 5-6, 8, 11-12, and 26-27 under 35 U.S.C. §112, second paragraph has also been withdrawn.

Claim 1 has been amended to recite "the recombinant protein variant" after the second occurrence of "naturally occurring allergen." Support for this amendment may be found throughout the specification and particularly in original claims 1, and 52-54.

Claims 25-26 and 30-32 have been amended to include reference to Accession Numbers. Support for these amendments may be found in the specification on at least pages 30 and 32.

Claims 52-54 have been amended to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue." Support for this amendment may be found throughout the specification and in original claims 1 and 19.

No new matter has been introduced in these amendments. Entry and consideration of these amendments is respectfully requested.

Amendments To The Specification

The specification has been amended at page 30, line 16; and at page 31, line 13 to replace "Q76H" with "E76Q." Support for this amendment may be found in the specification on page 30 and in Fig. 21 where residue 76 is described as being glutamic acid (E) in the reference sequence Accession No. AJ488060.

The Rejections Under the Second Paragraph of 35 U.S.C. § 112 Should Be Withdrawn

Claims 1-17, 19-32, 52-57, 59, 73, and 76-92 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office Action indicates that claim 1 is

indefinite because the term "protective immune response" has been defined broadly by Applicants. In response, Applicants respectfully point out that the term "protective immune response" (the complete term recited in pending claim 1) is particularly defined in this application, as it is used in the vaccine art. *See,* in particular, in the application as originally filed at page 43, lines 1-7. This definition makes it clear that the term, as used in this application, specifically refers to responses resulting in the production of mediator substances, such as cytokines and antibodies, that is well known to occur upon the stimulation of leukocytes (including T and B lymphocytes) and whose production neutralizes a particular antigen. Applicants therefore submit that the term is fully definite within the context of the application.

With regard to IgE antibodies mentioned by the Examiner, Applicants point out that IgG antibodies (and not IgE antibodies) are the ones that are generated in response to the inventive recombinant proteins and the IgG antibodies play a role in providing the desired protective immune response of the present invention. Additionally, the Examiner states that Applicants' definition also involves the activation of T cells, and that the number of stimulated T-cells necessary to raise a "protective" immune response is not discussed. Applicants note that there is no need to describe any particular number of T-cells or B cells that are stimulated using the inventive recombinant proteins. Applicants note that there are many examples throughout the specification of the use of "protective" consistent with its definition and as it is used in the vaccine art, for example with reference to the published application:

para 37: Introduction of mutations in the scaffold protein, introducing or modulating or eliminating existing antibody binding surface contours or epitopes homologous to structures of the allergen, results in creation of stable protein variants, ***capable of raising a protective immune response*** and with a lowered risk of inducing side-effects, since the mutated scaffold protein variant exhibits a lower antibody reactivity compared to the natural allergen.

"The purpose is to generate surface contours of the scaffold protein having similarity to the naturally occurring allergen in question, in order to enable stimulation of immune responses that will generate ***protective IgG antibodies*** with the ability to block IgE binding to the natural allergen and thereby alleviate or cure allergy symptoms."

para 42: The affinities of the IgE interactions should be reduced to a level limiting or abolishing the risk of triggering effector cell degranulation, while at the same time retaining the capacity to induce formation of ***protective antibodies reactive with the allergen*** in question.

para 79: The idea behind the invention is thus that a relatively small number of mutations are generally required in order to partly or fully establish allergen specific IgE recognizing contours on the surface of an appropriate scaffold protein. Such molecules have the potential ***of inducing new protective immune responses*** that can compete with IgE binding upon allergen exposure leading to a reduced risk of inducing IgE-mediated allergic responses

para 168: ***Protective immune response***: Raising a protective immune response means to alter the reaction of the immune system towards a naturally occurring allergen in order to avoid the adverse effects associated with allergy. The protective immune response is thought to be mediated largely by generation of a large number of IgG antibodies that presumably block the interaction between allergen and IgE antibodies. A protective immune response most likely also involves stimulation of T-cells.

The Examiner also alleges that with regard to claim 1, it is unclear what purpose is met by introducing an identical amino acid into a scaffold protein. We note that ***the identical amino acid reference is to the allergen***, and not the scaffold protein and believe that the Examiner is confused about the nature of the inventive recombinant protein. To arrive at the inventive recombinant proteins, a scaffold protein is initially selected that has a similar 3-D structure to the allergen, next the desired substitution mutations are introduced into the scaffold protein. These substitution mutations are selected and designed to be incorporated into the scaffold protein, based upon the corresponding sequence of the allergen. The substitutions introduce a mutation into the scaffold protein, which mutation/s correspond to either the same amino acid at the analogous position in the allergen, or a homologous amino acid residue of the analogous position in the allergen (would be a conservative change). The inventive recombinant proteins ***do not*** encompass recombinant scaffold proteins that are identical to the allergen, instead the inventive recombinant proteins are ***modified scaffold proteins***-- not identical to the native scaffold protein or to the naturally occurring allergen.

Additionally, the Examiner believes that the term "homologous" referring to an amino acid is unclear. Applicants point the Examiner to the definition for "homologous amino acid" provided in the specification at page 48, lines 15-23, and more specific definitions are provided throughout the Examples, in particular on pg 59, lines 5-7, pg. 60, lines 12-14, and lines 32-34 for Example 2.

The Examiner has rejected claims 25, 28, and 30-32, asserting that they are unclear due to the absence of SEQ ID NOs or a specific protein sequence reference. In the previous response, Applicants noted that these are dependent claims, and the base claims identify the reference proteins

as either Mal d 1 or Dau c 1. However, the Examiner has asserted that the claims are still not clear since there are several isomers of each protein and suggests adding reference to the specific amino acid sequence being mutated. Applicants point out that the mutations apply equally to isomers as to the reference protein, since the amino acid residues will be numbered in the same manner for the isomers. However, in order to expedite prosecution, Applicants are amending claims 25 and 29 to recite "wherein the *Mal d* 1 scaffold is *Mal d* 1 2620 with Accession No. AJ488060." Similarly, claims 30-32 have been amended to recite "wherein the Dau c1 has Accession No. T14325". Support for these amendments may be found on pages 30 and 32 of the specification.

The Examiner asserts that claim 26 recites an unclear mutation at position 76. Applicants note that this typographical error is actually in claim 25, and it has been amended to recite "E76Q" Support for the amendment may be found in the reference sequence described on page 30 of the specification. Applicants have corrected this error in two occurrences in the specification as noted in the remarks section above.

Finally, the Examiner alleges that claims 52-54 are unclear since they are drawn to variant proteins that have a primary mutation in a scaffold protein and that this mutated amino acid is either identical or homologous to a corresponding residue on the naturally occurring antigen. Applicants point the Examiner to the explanation provided above, which also applies to claims 52-54. Importantly, the claims do not encompass recombinant scaffold proteins that are identical to the allergen. Instead the inventive recombinant proteins are ***modified scaffold proteins***-- not identical to the native scaffold protein or to the naturally occurring allergen.

For all the foregoing reasons, Applicants respectfully submit that the rejections for indefiniteness under 35 U.S.C. § 112, paragraph 2, have been fully obviated and should be withdrawn.

The Rejections Under 35 U.S.C. § 102(b) Should Be Withdrawn

The Examiner has maintained the rejection of claims 1, 5-6, 9-10, 20-22, 55-56, and 59 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,583,046 to Valenta *et al.* ("Valenta"). Claims 1, 5-6, 8-9, 15, 20-24, and 52 have also been rejected under 35 U.S.C. § 102(b) as anticipated by Son *et al.*, Eur. J. Nutr., 1999, 38:201-215 ("Son"). In addition, the Examiner has

rejected claims 54 and 73 under 35 U.S.C. § 102(b) as anticipated by the publication of King *et al.*, J. Immun., 2001, 166(10):6057-6065 ("King").

A. The Legal Standard of Anticipation

Anticipation requires that each and every element of the rejected claim(s) be disclosed in a single prior art reference. See M.P.E.P. §2131 (8th Ed. Rev. 2, May 2004). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Every element of the claimed invention must literally present, arranged as in the claim. *Perkin Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 894, 221 USPQ 669, 673 (Fed. Cir. 1984).

B. Valenta Does Not Anticipate the Pending Claims

Valenta does not teach the use of a modified scaffold protein with a similar three-dimensional folding pattern to that of a desired natural allergen, nor does Valenta teach the insertion of mutations in the scaffold protein as recited in claim 1. Valenta teaches recombinant allergen proteins. In contrast, the present invention teaches the use of a scaffold protein which maintains the three-dimensional folding pattern of the allergen, and the introduction of point mutations into the scaffold protein, not into the allergen itself. Applicants note that the present claims do not encompass recombinant scaffold proteins that are identical to the allergen. Instead, the inventive recombinant scaffold proteins are modified when compared to the unmodified scaffold protein (i.e. the template) as well as when compared to the naturally occurring allergen.

Additionally, the claims require that the recombinant protein exhibit increased affinity and/or binding capacity to IgE antibodies specific to the naturally occurring allergen. Valenta does not teach recombinant mutant proteins that meet this requirement. Valenta does not teach recombinant proteins with structural similarity, *i.e.*, proteins with a similar tertiary structure. Applicants note that the Valenta results from IgE immunoblots are indicative only of binding conferred by an antigen binding site. *See* Valenta, col. 3, line 56 to col. 4, line 9. Having similar binding may or may not be due to a protein having an overall similar 3-D structure; it may be conferred by a protein with an antigenic site that confers this binding, while the protein does not

have a similar 3-D structure to the reference or native protein. Thus, Valenta does not require the three-dimensional folding pattern that the claims of the present invention require.

Furthermore, the polypeptides of Valenta have the same or similar antigenicity as the native allergen, *i.e.*, their binding affinity to IgE antibodies specific for the native allergen is the same or similar and do not exhibit increased binding. *See* col. 3, lines 17-30. The Examiner alleges that Valenta teaches:

> the results of IgE immunoblots, cross-inhibition tests, clinical tests and Northern (RNA) blots' and that these results 'indicate this invention provides polypeptides which exhibit the same or similar antigenicity as the related P14 pollen allergens of birch, alder, hazel, etc.[] The use of the term 'similar' suggests that the polypeptides are not completely identical in antigenicity, therefore being similar can comprise an increase in affinity or binding capacity (Fig. 1B, 13).

The terms "the same" or "similar" do not and cannot mean improved binding, which is greater binding. Additionally, the results cited by the Examiner are not quantitative tests (Fig. 1B and Fig. 13 is a dark immunoblot).

The present invention, on the other hand, claims recombinant proteins with an increased affinity and/or binding capacity to IgE antibodies that are specific to the naturally occurring antigen. *See,* for example, page 28, lines 10-21 Accordingly, Valenta does not teach all of the elements of the rejected claims, because it does not teach increased binding to IgE, Valenta cannot anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Valenta be withdrawn.

C. Son Does Not Anticipate the Pending Claims

The Examiner argues that Son teaches recombinant protein variants derived from Mal d 1 and Bet v 1. Applicants respectfully submit that Son does not teach all of the elements of the present invention. Son merely teaches, at best, the use of native allergens in which point mutations are inserted. See pages 202, and 204-205. In contrast, the present invention teaches the ***use of a scaffold protein*** which ***maintains the three-dimensional folding pattern of the allergen***, and ***the introduction of point mutations into the scaffold protein***, not into the allergen itself. See page 11, lines 15-27. In further contrast to the present invention, although Son teaches that point

mutations inserted into the native allergen can cause a reduction in IgE binding capacity (see page 208), Son does not teach that mutations inserted into a scaffold protein would increase or decrease the binding affinity of IgE specific to the native allergen. See page 24, line 26 to page 25, line 16. Insertion of point mutations according to the method of Son creates a risk of destabilizing the three-dimensional structure of the molecule. *Id.*

In particular, we note that the Son mutants are Ser112Pro, Ser111Cys, or Ser111Pro mutants. However, these mutations are ***not*** identical or homologous to the corresponding amino acid residues, and therefore do not satisfy that requirement of Applicants' pending claims. Indeed, Son actually teaches that these mutations are not homologous. For example, Son hypothesizes, on page 214 of that reference, that serine may be part of an epitope. Son then goes on to note that "proline is known to cause major structural changes in the protein fold, and the drastically decreased IgE reactivity of the proline mutants may also reflect major changes in the tertiary fold of the allergens." Likewise, the Ser111Cys mutant is likely to have a structural change compared to the native Mal d 1 isoform. Thus, in contrast to the Examiner's assertion that the single point mutations of Son have a decreased risk of destabilizing the three-dimensional structure of the scaffold protein, the reference actually contemplates major structural changes due to a single proline substitution.

Applicants' specification teaches that mutations from Serine to either Cysteine or Proline are not homologous substitutions. *See*, for example, in the specification at page 48, lines 15-23; on page 59, lines 5-7; on page 60, lines 12-14 and 32-34; in Example 2; and throughout the Examples. In contrast to Son, the present invention is directed to the introduction of mutations that preserve the three dimensional structure of the protein. See page 11, lines 15-27.

Accordingly, Son does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under Son be withdrawn.

D. King Does Not Anticipate the Pending Claims

The Examiner argues that King teaches modified recombinant allergens consisting of a "host protein" which is used as a scaffold protein, which is fused with a "guest allergen." Applicants

would like to point out that claim 54 has been amended (inadvertently omitted in the previous response) to recite "comprises two or more primary mutations spaced by at least one non-mutated amino acid residue," as is recited in the other independent claims. Analogous amendments have been made in claims 52 and 53. Applicants note that King is directed to hybrid constructs wherein a scaffold protein is substituted with relatively long stretches of amino acids of a native allergen, and therefore does not contain "two or more primary mutations spaced by at least one non-mutated amino acid residue." Neither King nor Applicants' recombinant proteins would encompass the native allergen itself.

In view of the present amendments, King does not teach all of the elements of the rejected claims, and therefore does not anticipate the present application. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) under King be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,
By

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